Program/Abstract # 92
The oxygen sensor fatiga controls *Drosophila* oogenesis through the regulation of FoxO
Julieta Acevedo, Pablo Wappner
Buenos Aires, Argentina

When cells are subjected to hypoxia they suffer deep changes in gene expression that tend to minimize the hypoxia effect and to restore energy homeostasis. Hypoxic gene induction is mainly mediated by the Hypoxia Inducible Factor (HIF), a heterodimeric α/β transcription factor composed of two bHLH-PAS subunits. While HIF-β is constitutively expressed, HIF-α subunit is tightly regulated by oxygen. Oxygen regulation is mediated by specific Prolyl-4-hydroxylases (PHDs) that hydroxylate HIF-α in two proline residues utilizing O2 as a co substrate of the reaction. Hydroxylated HIF-α is targeted for degradation at the 26S proteasome. In our lab we have identified Sima and Fatiga (Fga) as the HIF-α and PHD fly homologues respectively. We have shown that whereas Sima mutants are fully viable and fertile in normoxia, Fga mutants are lethal at different developmental stages. We demonstrated that Fga lethality is due to Sima over accumulation as Fga–Sima double mutants recover viability. Interestingly despite being fully viable Fga–Sima double mutants are sterile indicating that an alternative Fga target, different from Sima, is involved in the *Drosophila* ovary development. We have studied in detail the Fga–Sima ovary phenotype and found that mutant follicles are unable to carry out the transition from polyteny to polyploidy that occurs during normal *Drosophila* oogenesis. We demonstrated that over-activation of the transcription factor FOXO accounts for the ovary phenotype of the Fga–Sima double mutants, since in Fga–Sima–Foxo triple mutants ovaries were normal. Our results demonstrate that the oxygen sensor Fga negatively regulates FOXO thus controlling *Drosophila* oogenesis.

doi:10.1016/j.ydbio.2011.05.115

Program/Abstract # 93
Endoplasmic reticulum remodeling tunes IP3 receptor sensitivity
Lu Sun[a], Fang Yu[b], Khaled Machaca[b]
[a]*Weill Cornell Medical College Qatar, Doha, Qatar*
[b]*Doha, Qatar*

The activation of vertebrate development at fertilization relies on IP3-dependent $Ca2^{+}$ release, a pathway that is sensitized during oocyte maturation. Here we show that remodeling of the endoplasmic reticulum (ER) tunes IP3-dependent $Ca2^{+}$ release sensitivity. The ER restructures during meiosis to form large "ER patch" sub-domains, within which IP3 receptors exhibit increased sensitivity. ER patches are dynamically restructured and IP3 receptor mobility is not altered in these ER sub-domains. This argues that IP3 receptor sensitization is due to the increased density of IP3 receptor within the three-dimensional space of an ER patch, through enhanced cooperativity at sub-threshold IP3 concentrations, a conclusion supported by mathematical modeling. Hence, ER remodeling represents a novel mechanism of modulating IP3 receptor function that is distinct from the previously described lateral clustering of IP3 receptors.

doi:10.1016/j.ydbio.2011.05.116

Program/Abstract # 94
The Ras/Erk signal transduction cascade mediates the morphogen-like activities of FGF8 in the developing telencephalon
Forrest O. Gulden[a], Elizabeth A. Grove[b]
[a]*University of Chicago Committee on Neurobiology, Chicago, IL, USA*
[b]*Department of Neurobiology, University of Chicago, Chicago, IL, USA*

FGF8 is secreted from the anterior pole of the telencephalon, diffuses through the entire dorsal telencephalon, and patterns the neocortical area map along its anterior to posterior (A/P) axis. Both the Ras/Erk and Akt signal transduction cascades are active at this time in the neocortical anlage. It is unclear, however, which signal transduction pathway mediates the morphogenic activity of FGF8 in the dorsal telencephalon. We are using a telencephalic explant system to address this question. We expose neocortical explants harvested from embryos at 10.5 days post conception to several concentrations of FGF8b. Explants are maintained in culture and harvested at several time points. Some explants are processed with in situ hybridization to detect expression of different genes that, in vivo, are indicative of A/P position in the neocortical primordium. Other explants are processed using Western blots to characterize levels of phosphorylated MAPK and Akt in response to different concentrations of FGF8. Experiments are then repeated in the presence of inhibitors of the Ras/Erk and PI3K/Akt transduction pathways. Our results indicate that phosphorylation levels of MAPK, but not Akt, correlate with the levels of FGF8b applied and with the regulation of specific genes in the explants. In accordance with a role in transducing the morphogenic effects of FGF8, activation of the MAPK pathway is both dose- and time-dependent. Activation of the Akt pathways is not. Additionally, the extent of MAPK activation is greater than the extent of Akt activation. Combined, these data demonstrate that the Ras/Erk signal transduction cascade mediates the morphogen-like activities of FGF8 in the developing telencephalon.

doi:10.1016/j.ydbio.2011.05.117

Program/Abstract # 95
Expression of EGF-responsive ERK5 in embryonic mouse submandibular glands
Masanori Kashimata[a], Noriko Koyama[a], Toru Hayashi[a], Edward Gresik[b]
[a]*Asahi University School of Dentistry, Dept of Pharmacology, Mizuho, Japan*
[b]*Sophie Davis School of Biomedical Education, New York, NY, USA*

Growth factors and their receptors regulate development of many organs through activation of multiple intracellular signaling cascades including a mitogen-activated protein kinase (MAPK). Extracellular regulated kinase (ERK)1/2, a classic MAPK family member, is expressed in the fetal mouse submandibular gland (SMG) and stimulates branching morphogenesis. ERK5, also called big mitogen-activated protein kinase 1, is a recently discovered new member of MAPK super family, and its biological roles are still largely unknown. In this study, we investigated the expression and function of ERK5 in developing fetal mouse SMGs. Western blotting analysis showed that the expression pattern of ERK5 was different from the pattern of ERK1/2 in developing fetal SMGs. Phosphorylation of ERK1/2 was strongly induced by epidermal growth factor (EGF) in SMG rudiments at embryonic day 14 (E14), E16 and E18. However, ERK5 phosphorylation by EGF was clearly observed at E14 and E16, but not at E18. Branching morphogenesis of cultured E13 SMG rudiments was strongly suppressed by administration of U0126, an inhibitor for ERK1/2 activation, whereas the phosphorylation of ERK5 was not inhibited by U0126. BIX02188, a specific inhibitor for ERK5 activation, also inhibited branching morphogenesis in cultured SMG rudiments. These results show that EGF-responsive ERK5 is expressed in developing fetal mouse SMG, and suggest that both ERK1/2 and